Treatment of Women With Epilepsy
By Mona Sazgar, MD, FAES

ABSTRACT
PURPOSE OF REVIEW: This article provides the latest information to guide practitioners in counseling and treating women with epilepsy.

RECENT FINDINGS: There is an increasing body of literature on the multidirectional effects of sex hormones on seizure frequency and severity and of seizures altering areas of the brain involved in neuroendocrine function. Ongoing pregnancy outcome data from pregnancy registries and meta-analysis of observational studies have provided key information on the safety of using antiseizure medications during pregnancy and the risk to the fetus.

SUMMARY: In treating and counseling women with epilepsy from puberty to menopause, it is important to understand the complex interactions of sex hormones, seizures, and antiseizure medications on reproductive health and pregnancy outcomes.

INTRODUCTION
Epilepsy is estimated to affect 70 million people worldwide\(^1,2\) and is one of the most common neurologic diseases globally. Nearly 1.5 million women of childbearing age in the United States live with epilepsy, and each year approximately 24,000 give birth. Specific challenges arise in caring for women with epilepsy throughout their life cycle from menarche to menopause. Important considerations in the care of women with epilepsy include whether antiepileptic drugs (AEDs) interact with contraceptives; how AEDs impact fertility, teratogenic risk, and libido; whether seizures and AED concentrations change during pregnancy, postpartum, and lactation; and the risk of osteoporosis associated with AEDs and epilepsy.

CATAMENIAL EPILEPSY
The term *catamenial* is derived from the Greek word *katamenios*, meaning “monthly.” In 1857, Sir Charles Locock first described that some seizures are associated with the menstrual cycle.\(^3,4\) William Gowers in 1881 reported that the majority of women with epilepsy in his practice had reported a worsening of their seizures perimenstrually.\(^5,6\) Women with catamenial epilepsy have a cyclic exacerbation of their seizures at certain points in their menstrual cycle that are attributed to fluctuations in their sex hormones.\(^7,8\) Estrogen and progesterone variations throughout the menstrual cycle and their neuroactive effects on brain structures with epileptic potential are thought to be the principal behind...
catamenial epilepsy. This condition is reported in at least one-third of women with epilepsy. Herzog and colleagues\textsuperscript{9,10} proposed existence of three patterns of catamenial seizure exacerbation (\textbf{FIGURE 6-1} and \textbf{TABLE 6-1}): perimenstrual (C1: days –3 to 3) and periovulatory (C2: days 10 to –13) in ovulatory cycles and the entire luteal phase (C3: day 10 of one cycle to day 3 of the next cycle) in anovulatory cycles, where day 1 is the first day of menstrual flow and day 14 is the day of ovulation. The diagnosis is made by using seizure diaries and charting the time of ovulation (by using basal body temperature or ovulation kits) and menstruation for three cycles. If most seizures (twofold or higher) occur during one of the above periods, a diagnosis of catamenial epilepsy is made.

\textbf{MECHANISM OF CATAMENIAL EPILEPSY}

Estrogen and progesterone have neuroactive properties, meaning that they can alter neuronal excitability and seizure susceptibility by their effect on brain structures. As a rule, estrogens are proconvulsant and progesterone anticonvulsant. Progesterone’s reduced metabolite, allopregnanolone, is a potent positive allosteric modulator of \(\gamma\)-aminobutyric acid type A (GABA-A) neurotransmission,\textsuperscript{11} which may mediate anticonvulsant potential. In rodent models of catamenial epilepsy developed by Reddy and colleagues,\textsuperscript{12} withdrawal of progesterone or allopregnanolone, mimicking the premenstrual state, enhanced neuronal excitability and seizures.\textsuperscript{12}

Evidence exists for moderate proconvulsant activity of estrogen-containing compounds. Ethinyl estradiol significantly increased seizure frequency and severity in kindled female mice.\textsuperscript{13} Estradiol may potentiate seizures by increasing the density of dendritic spines and N-methyl-D-aspartate (NMDA) receptor-containing excitatory synapses in the hippocampus. Estradiol may also potentiate non-NMDA kainate-mediated and quisqualate-mediated neurotransmission,\textsuperscript{14–16} which may explain the increase in seizure risk with exposure to oral contraceptives reported by

\textbf{FIGURE 6-1}

Patterns of catamenial epilepsy. \textit{A}, The normal menstrual cycle. \textit{B}, The inadequate luteal phase cycle. The three patterns of catamenial epilepsy are (1) perimenstrual (C1, day –3 to 3), (2) periovulatory (C2, day 10 to –13) for the normal ovulatory cycles, and (3) the entire second half of the cycle for inadequate luteal phase (C3, day 10 to 3). Day 1 is the first day of menstrual flow, and day 14 is the day of ovulation.

\(F\) = follicular phase; \(L\) = luteal phase; \(M\) = menstruation; \(O\) = ovulation

Reprinted with permission from Herzog AG, Seizure.\textsuperscript{10}

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Herzog and colleagues.\textsuperscript{17–19} This large, community-based survey found that 28.2% of women with epilepsy reported a change in seizures when using hormonal contraception, with the relative risk of seizure being 4.5 times higher in women using hormonal contraception than in women using nonhormonal contraception.

Estrogen effects on seizure exacerbation are complex. The dose, route of administration, acute versus chronic administration, and natural hormonal environment may change its proconvulsant potential.\textsuperscript{20}

Finally, antimüllerian hormone, another neuroactive peptide that is a measure of ovarian reserve and follicular activity and a member of the transforming growth factor β family, has been implicated as having seizure-protective properties. Women with epilepsy who have active seizures have a lower concentration of antimüllerian hormone compared with those without seizures and healthy controls,\textsuperscript{21} and the hormone protects neurons against NMDA-mediated neurotoxicity both in vitro and in vivo.\textsuperscript{22,23} The antimüllerian hormone receptor is expressed in several brain regions that are also involved in epileptic networks, including the hippocampus, cortex, and hypothalamus. Further studies are needed to establish whether antimüllerian hormone is protective against seizures in women with epilepsy.\textsuperscript{24}

**THE HYPOTHALAMIC–PITUITARY–OVARIAN AXIS AND EPILEPSY**

Brain regulation of sex hormones occurs via the hypothalamic-pituitary-ovarian axis (\textbf{FIGURE 6-2}). Gonadotropin-releasing hormone produced by the hypothalamus stimulates the production of follicle-stimulating hormone and luteinizing hormone for secretion by the anterior pituitary gland. Follicle-stimulating hormone stimulates the growth of ovarian follicles, which, in turn, secrete estradiol (the main form of estrogen). The dominant ovarian follicle develops into the oocyte. This is called the follicular phase (days 1 to 14).

Estrogen production results in negative feedback, reducing follicle-stimulating hormone but stimulating gonadotropin-releasing hormone. Gonadotropin-releasing hormone stimulation leads to a luteinizing hormone surge, further oocyte maturation, ovulation, and the conversion of the follicle to corpus luteum, signaling the end of the follicular phase and the start of the luteal phase.

**TABLE 6-1**

<table>
<thead>
<tr>
<th>Patterns of Catamenial Epilepsy$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perimenstrual or C1 Pattern</strong></td>
</tr>
<tr>
<td>◆ Significant increase in average seizure frequency around day -3 to day 3 of the menstrual cycle compared with the rest of the menstrual cycle</td>
</tr>
<tr>
<td><strong>Periovulatory or C2 Pattern</strong></td>
</tr>
<tr>
<td>◆ Significant increase in average seizure frequency during ovulation around days 10 to 13 compared with the rest of the menstrual cycle</td>
</tr>
<tr>
<td><strong>Inadequate Luteal Phase or C3 Pattern</strong></td>
</tr>
<tr>
<td>◆ Significant increase in average seizure frequency between day 10 of one cycle and day 3 of the next cycle, which includes ovulatory, luteal, and menstrual phases in women with an inadequate and anovulatory luteal phase</td>
</tr>
</tbody>
</table>

$^a$ Data from Herzog AG, Seizure.\textsuperscript{10}
Corpus luteum secretes progesterone, which inhibits gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone production. In the absence of pregnancy, corpus luteum regresses, and both progesterone and estradiol decline, resulting in menstruation. The cycle repeats as lower levels of progesterone decrease gonadotropin-releasing hormone inhibition.

The hypothalamic-pituitary-ovarian axis regulation is affected by the abnormal neurophysiology of seizures, and the hypothalamic-pituitary-ovarian–associated hormones are affected by medications used to treat seizures in women with epilepsy. Ictal and interictal discharges can disrupt the normal activity of brain structures, including the limbic system, amygdala, hypothalamus, and pituitary gland. Hepatic enzyme–inducing AEDs, specifically cytochrome P450 3A4 (CYP3A4) inducers, affect the metabolism of endogenous sex hormones and thyroid hormones and, therefore, contribute to the dysregulation of the hypothalamic-pituitary-ovarian axis.

TREATMENT OF CATAMENIAL EPILEPSY

No specific treatment is approved by the US Food and Drug Administration (FDA) for catamenial epilepsy. The treatment is usually divided into hormonal and nonhormonal. Acetazolamide, which has been in use for more than 50 years, is one of the oldest treatment options for catamenial epilepsy. There have not been any randomized clinical trials to prove the efficacy of acetazolamide in treating catamenial epilepsy.

Benzodiazepines, such as clonazepam and clobazam, are used in the treatment of seizure clusters during hormonally related exacerbation of seizures. Benzodiazepines are positive allosteric modulators of the GABA-A receptor, and of the benzodiazepines, clobazam has a particularly broad spectrum of efficacy against a variety of seizure types. In a double-blind, placebo-controlled crossover study, clobazam resulted in complete control in most women during the 10-day trial period. In this study, clobazam was effective when used at a dose of 20 mg/d to 30 mg/d, administered intermittently starting 2 to 4 days.
before menses. The most common adverse effects of clobazam are sedation and depression.

Certain antiseizure medication doses can be temporarily increased during the catamenial seizure exacerbation period. This approach may not be safe with some antiseizure medications, such as phenytoin and carbamazepine. Synthetic progestin depot-medroxyprogesterone acetate at a dose of 150 mg every 3 months has been used for reducing seizure exacerbation in catamenial epilepsy. Reductions in seizure frequency of up to 39% over a 1-year period have been reported. A risk of osteoporosis occurs with the prolonged use of depot-medroxyprogesterone acetate, and the delay to conception with depot-medroxyprogesterone acetate may last up to 1 year.

A National Institutes of Health–sponsored randomized, double-blind, placebo-controlled Phase 3 multicenter clinical trial by Herzog and colleagues assessed the response to treatment with natural progesterone lozenges in women with medically refractory catamenial partial epilepsy. Patients were randomly assigned 2:1 to progesterone or placebo. Overall results were negative for a beneficial effect, but a post hoc analysis showed a significantly higher responder rate in women with perimenstrual seizure exacerbation (C1). Progesterone may provide a clinically important benefit for this subset of women with perimenstrual

### TABLE 6-2 Suggested Treatment Options in Women With Catamenial Epilepsy

1 **Determine True Catamenial Epilepsy**
   A. Establish whether the seizures are, in fact, catamenial in nature by using seizure diaries. Ask the patient to chart daily the seizure type and frequency with simultaneous recording of ovulation and menstruation status using an ovulation kit or basal body temperature recording for three menses.

   B. Determine whether there is an increase in the number and severity of seizures by twofold or greater during the specific days of the patient’s menstrual cycle and establish C1, C2, or C3 type of catamenial epilepsy.

2 **Choose One of the Options Below**

   A. **Progesterone lozenges/natural progesterone for C1 pattern**
      For the C1 type, consider using progesterone lozenges 200 mg 3 times daily around the days of seizure exacerbation or days 14 to 28 of the cycle.

   B. **Synthetic progestin**
      Consider oral daily synthetic progestin or intrauterine devices with progestin versus depot-medroxyprogesterone acetate.

   C. **Acetazolamide**
      Consider using at 250 mg twice daily or 500 mg twice daily to be taken around the 7–10 days of seizure exacerbation as determined by the seizure diary.

   D. **Clobazam**
      20 milligrams to 30 mg divided twice a day or one dose at night for 10 days, starting 2 days before and throughout the identified seizure exacerbation dates.

   E. **Small increase in baseline antiepileptic drugs**
      These can be taken approximately 2 days before the identified period of seizure exacerbation for up to 10 days. Be cautious about phenytoin, carbamazepine, or other medications with a higher risk of toxicity.
catamenial epilepsy, which is the most prevalent form (TABLE 6-1). TABLE 6-2 shows a suggested treatment algorithm for catamenial epilepsy.

REPRODUCTIVE DISORDERS

Reproductive disorders in women with epilepsy may result from direct effects of seizures or secondary to use of certain antiepileptic drugs.

Direct Effects of Seizures

A higher rate of reproductive disorders, including polycystic ovary syndrome, infertility, and decreased libido, occurs in women with epilepsy. Menstrual disorders are estimated to occur in one-third of women with epilepsy compared with 12% to 14% of women in the general population.35 Polycystic ovary syndrome is characterized by enlarged ovaries with multiple small cysts and a hypervascularized, androgen-secreting stroma leading to the associated signs of androgen excess (hirsutism, alopecia, acne), obesity, and menstrual cycle disturbance (oligomenorrhea or amenorrhea).34 It occurs in 4% to 7% of women of reproductive age in the general population but in 10% to 25% of women with epilepsy.35,36 The amygdala has reciprocal connections with the hypothalamus, and seizures originating from the mesial temporal lobe can disrupt the gonadotropin-releasing hormone-producing cells in the preoptic area of the hypothalamus, resulting in abnormal luteinizing hormone and follicle-stimulating hormone levels and, therefore, abnormal levels of sex hormones and sexual dysfunction. Herzog and colleagues37 studied 50 consecutive women with temporal lobe epilepsy and found that 56% of them reported amenorrhea, oligomenorrhea, or abnormally long or short menstrual cycle intervals, and 68% showed reproductive endocrine disorders, such as polycystic ovary syndrome, hypoandrogenism, premature menopause, and hyperprolactinemia.

The fertility data in women with epilepsy are conflicting. The Rochester population study of residents for the years 1935 to 1974 found the fertility rate was reduced to 85% in women with epilepsy.38 Another population study in Iceland found no difference in birth rates of women with epilepsy compared with sex-matched residents without epilepsy except in patients with epilepsy with mental retardation and cerebral palsy.39 More recently, Pennell and colleagues40 conducted an observational cohort study that compared the fertility rate in 89 women with epilepsy without previously known infertility with 108 control women. They found no difference in achieving pregnancy, sexual activity, ovulatory rates, time to pregnancy, and live birth rates among the two groups. Fertility is affected by multiple factors, including the social and psychological state and frequency of unprotected intercourse.

Antiepileptic Drug Effects

AEDs are known to cause endocrine side effects resulting in abnormalities in fertility, thyroid hormones, sexual function, and bone health. Microsomal hepatic enzyme-inducing AEDs, such as phenytoin, carbamazepine, and phenobarbital, can reduce the circulating bioavailable steroid hormones and, therefore, increase sex hormone-binding globulin concentrations.41 Valproic acid is also known to cause endocrine side effects. In 1993, Isojärvi conducted the first systematic study of 238 women with epilepsy receiving valproic acid monotherapy. Approximately 45% of these women had menstrual disorders, and of those, 90% had polycystic ovary syndrome or hyperandrogenism, or both.42
The risk of developing polycystic ovary syndrome and high testosterone levels was age dependent and highest in women 26 years old and younger. In a prospective study, an increase in serum testosterone and androstenedione levels was seen in half of the women within 3 months of starting valproic acid therapy.\(^4\) The endocrine adverse effects of valproic acid are at least partly reversible. Valproic acid–induced weight gain may exacerbate its endocrine effects.

Sexual dysfunction and decreased libido and satisfaction with sex lives are also reported in women taking enzyme-inducing AEDs, such as carbamazepine and phenytoin.\(^4\) Mattson and colleagues\(^4\) reported sexual dysfunction and decreased libido in 16% of patients with epilepsy after starting monotherapy.

### TABLE 6-3

**Antiepileptic Drugs and Contraceptive Failure**

**Antiepileptic Drugs Causing Contraceptive Failure**
- Carbamazepine
- Clobazam
- Eslicarbazepine acetate
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Primidone
- Rufinamide

**Antiepileptic Drugs Causing Contraceptive Failure at Higher Doses**
- Felbamate
- Perampanel
- Topiramate

**Antiepileptic Drugs With No Known Effect on Contraceptive Failure**
- Clonazepam
- Ethosuximide
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam\(^a\)
- Retigabine/ezogabine
- Tiagabine
- Valproate\(^b\)
- Vigabatrin
- Zonisamide

\(a\) Increased testosterone concentrations reported in men on levetiracetam.

\(b\) Decreased free testosterone concentrations in men and increased androgen concentrations in women taking valproate.
with phenobarbital, 12% after starting phenytoin, and 13% after starting carbamazepine.

The full endocrine side effect profile of newer AEDs is unknown. Lamotrigine is not found to cause endocrine side effects. In fact, switching from valproic acid to lamotrigine resulted in normalization of endocrine function after a year. Levetiracetam can reduce basal estrogen secretion from ovarian follicles, but it does not affect the gonadotropin-stimulated estrogen secretion. To date, no clinically significant reproductive endocrine side effects have been associated with the use of levetiracetam in women or prepubertal children with epilepsy. However, there have not been any randomized studies assessing the potential endocrine side effects of other newer antiseizure medications.

CONTRACEPTION

A variety of hormonal contraception methods are available, including oral contraceptive tablets, topical patches, IM depot injections, implants, and intrauterine devices. Combined oral contraceptives contain both synthetic estrogen and progestin. Contraceptives work with inhibition of ovulation or fertilization. The progestin component is responsible for the contraceptive effect of combined oral contraceptives, including inhibition of ovulation, increased viscosity of the cervical mucus, and reduced endometrial suitability for ovum implantation. The oral contraceptive failure rate is 1% in healthy women but 3% to 6% in the population of women with epilepsy. The Epilepsy Birth Control Registry, a web-based survey, reported data on 1,144 women with epilepsy aged 18 to 47 years. Most (78.9%) reported having at least one unintended pregnancy, and 65.0% of their pregnancies were unplanned. In comparison, in 2011, nearly half of pregnancies (45% or 2.8 million of 6.1 million) in the United States were unintended. Others found that fewer than 55% of women with epilepsy plan their pregnancy, and contraceptive failure is the cause of one in four unplanned pregnancies. The consequences can be devastating considering that women with epilepsy may be taking antiseizure medications with significant teratogenic side effects. Neurologists should be aware of the complex and, at times, bidirectional interactions between AEDs and hormonal contraception.

Enzyme-inducing AEDs, such as phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, and eslicarbazepine acetate, can result in contraceptive failure because these drugs lower the level of the progestin component of hormonal contraceptives through CYP3A4 induction. Perampanel, felbamate, and topiramate are less potent hepatic enzyme inducers and can cause contraceptive failure at higher doses. However, levetiracetam, gabapentin, pregabalain, vigabatrin, tiagabine, zonisamide, and lacosamide have no known interactions with oral contraceptives. Women who take enzyme-inducing AEDs may be at risk of contraceptive failure when taking the progestin-only pills. Theoretically, enzyme-inducing AEDs may reduce the efficacy of depot-medroxyprogesterone acetate injections, and it is common practice to administer the injections every 10 weeks in women using enzyme-inducing AEDs, as opposed to the recommended 12-week intervals for women in the general population. Women with epilepsy receiving enzyme-inducing AEDs who receive levonorgestrel subdermal capsules are also at risk of contraceptive failure. Two of nine women with epilepsy who received enzyme-inducing AEDs became pregnant in 1 year.
A study comparing contraceptive efficacy in women receiving levonorgestrel subdermal implants, while no pregnancies occurred in 10 control women with epilepsy.57 Both women were taking phenytoin, and their plasma concentrations of levonorgestrel were low at the time of conception. In a separate report, there were significant reductions in etonogestrel concentrations seen in 10 women receiving carbamazepine 600 mg/d who were concurrently using a contraceptive implant.53

Intrauterine devices (IUDs) are T-shaped devices that are fitted into the uterus. The two common types are copper IUDs (nonhormonal) and levonorgestrel-releasing IUDs. The copper IUD prevents pregnancy by releasing into the uterus a small amount of copper, which is toxic to sperm, and the levonorgestrel-releasing IUD causes a thickening of the cervical mucus, thereby blocking sperm passage. IUDs are highly efficacious and are not affected by enzyme-inducing AEDs, making them a reasonable form of contraception for women with epilepsy.

PREGNANCY AND PERINATAL COUNSELING
Approximately 24,000 women with epilepsy become pregnant each year. In the majority of women with epilepsy, pregnancy has no effect on their seizure frequency; therefore, if seizures are well controlled, they are likely to remain so during pregnancy. However, in approximately 20% to 35% of pregnancies in women with epilepsy, an increased seizure frequency occurs during pregnancy.58,59

In an analysis of data from the European Registry of Antiepileptic Drugs and Pregnancy (EURAP), an international AED and pregnancy registry, 33.4% of pregnant women experienced seizures during pregnancy. Seizure frequency was unchanged in 70.5%, reduced in 12.0%, and increased in 15.8% of women with epilepsy.60 The Australian Pregnancy Registry for women with epilepsy found that, between 1998 and late 2016, seizures had occurred during pregnancy in approximately 43%. Seizures of any type occurred in 78.4% of pregnancies when seizures had occurred in the previous year (active epilepsy) and in 22.3% of those associated with inactive epilepsy. From these data, having a seizure disorder that was active in the year before pregnancy and in early pregnancy appears to be the best predictor of seizure recurrence during pregnancy.61

Cagnetti and colleagues62 reported better seizure control during pregnancy in women with catamenial epilepsy compared with women with epilepsy in general. They prospectively followed women referred to their Epilepsy Center for pregnancy planning. In this study, 59 women with catamenial epilepsy and 215 with noncatamenial epilepsy were included. Forty-seven women (79.7%) with catamenial epilepsy and 48 women (22.3%) with noncatamenial epilepsy remained seizure free throughout pregnancy.62

The reasons for seizure recurrence during pregnancy are multifactorial, including lowering or stopping antiseizure medications because of fear of harming the baby, hormonal fluctuations, and a higher estrogen-to-progesterone ratio especially in weeks 8 to 16 of pregnancy, sleep deprivation, and psychosocial stress. The most common cause of seizure recurrence in pregnancy, however, is likely reduced plasma concentration of AEDs and changes in AED metabolism. The plasma AED concentration fluctuates during pregnancy because of several physiologic reasons, including increased renal clearance, altered hepatic absorption, increased plasma volume of distribution, and hepatic enzyme induction by steroid hormones.63 A reduction in AED blood levels during
pregnancy by 35% or more compared with baseline levels may be the cause of an increase in seizures. During pregnancy, the dose of antiseizure medications should be adjusted based on the patient’s seizure history and prepregnancy levels.

Lamotrigine metabolism through hepatic glucuronidation is enhanced during pregnancy by elevated concentrations of sex hormones. Declining plasma concentrations of lamotrigine during pregnancy, therefore, may be associated with increased seizure frequency in more than 40% of patients. Worsening seizure control in the second and third trimester is more common in women taking lamotrigine than those taking carbamazepine or valproic acid. Lamotrigine clearance during pregnancy is 2 to 3 times higher than before pregnancy. The levels after delivery reach prepregnancy levels within 1 to 3 weeks.

Based on an analysis of data from six hospitals in Norway and Denmark, zonisamide serum concentration may fall by more than 40% during pregnancy. Reimers and colleagues found that the lowest zonisamide serum concentration occurred in gestational months 6 to 9, with significant interindividual variability, and 4 of 10 patients who were previously seizure free developed breakthrough seizures during pregnancy. The plasma concentration of the active metabolite of oxcarbazepine declines by 36% to 50% in the late stages of pregnancy and is associated with increased seizure frequency in 50% of women. Therefore, an adjustment in the dose of oxcarbazepine is necessary during pregnancy. The elimination rate of levetiracetam is significantly increased during pregnancy because of increased renal glomerular filtration in late pregnancy. Therapeutic drug monitoring and adjustment of the dose, therefore, is needed.

The American Academy of Neurology (AAN) practice guidelines suggest checking AED levels at baseline before conception and monthly thereafter. Dose adjustments should be considered to maintain an effective and stable level throughout pregnancy, at least for women with epilepsy who are taking lamotrigine, oxcarbazepine, levetiracetam, carbamazepine, and phenytoin. Despite limited evidence for changes in levels of other AEDs during pregnancy, AED levels should be regularly monitored during each trimester of pregnancy because of the potential for altered AED bioavailability, metabolism, and clearance.

Risks to the Fetus Because of Maternal Seizure Recurrence

Women with epilepsy who experience seizures during their pregnancy are at increased risk of delivering preterm, low-birth-weight, and small-for-gestational-age newborns. A nationwide population-based study of 1016 women with epilepsy in Taiwan reported that epileptic seizures during pregnancy were independently associated with an increased risk of adverse outcomes, with a 1.36-fold increased risk of low birth weight, 1.63-fold increased risk of preterm delivery, and 1.37-fold increased risk of small-for-gestational-age babies. This seizure-related risk may be related to fetal hypoxia, acidosis, decreased blood flow to the placenta, deceleration of fetal heart rate, and trauma as a result of a maternal fall. In another study, frequent maternal tonic-clonic seizures during pregnancy were associated with a lower verbal IQ in their offspring. To avoid these harmful effects of convulsive seizures on the fetus, controlling seizures during pregnancy is crucial. The benefits of using AEDs during pregnancy may outweigh the potential teratogenic side effects.

In counseling women with epilepsy who plan to become pregnant, practitioners should discuss the need for staying on antiseizure medication,
simplifying the medication regimen, attempting monotherapy, and selecting medications with more favorable side effect profiles. Baseline prepregnancy AED levels should be obtained to guide adjustment of the dose during pregnancy. Monthly levels during pregnancy will help in detecting a significant decrease in levels. In case of any seizure recurrence or fall, the patient should be evaluated at the obstetrics clinic to ensure maternal and fetus well-being. The patient with active epilepsy should be managed by a team of high-risk obstetricians and epileptologists working together to manage her throughout her pregnancy, delivery, and immediate postpartum period.

**Risk of Birth Defects or Fetal Death Because of Antiepileptic Drugs**

Most women with epilepsy give birth to healthy offspring, but since the 1960s there have been reports that children of women taking AEDs during pregnancy may be at increased risk of birth defects, premature birth, low birth weight, and low Apgar scores. A systematic review of 59 studies found that the overall frequency of major congenital malformations was 3 times greater in children of women with epilepsy than without epilepsy. This increased risk could be attributed to either AEDs or maternal epilepsy. In a pooled analysis of data from 26 studies, the rate of major congenital malformations was highest in children of AED-treated women with epilepsy (6.1%) when compared to children of untreated women with epilepsy (2.8%) and control population women (2.2%). Polytherapy (6.8%) resulted in a higher rate of fetal malformation than monotherapy (4%), and the risk was dose dependent at higher versus lower doses of valproic acid (>700 mg/d), carbamazepine (>400 mg/d), phenobarbital (>150 mg/d), and lamotrigine (>300 mg/d).

Multiple worldwide AED pregnancy registries prospectively collect data on women with and without epilepsy who receive AEDs to determine risk for adverse pregnancy outcomes and major congenital malformations. The North American AED Pregnancy Registry (NAAPR) recently reported on the risk of major congenital malformation for 11 AEDs for pregnancy outcomes of 9294 women with and without epilepsy who were receiving AEDs for any reason between February 1997 and December 2015, as summarized in FIGURE 6-3. Major malformations were defined as overt structural, consequential abnormalities identified between birth and age 5 days. AEDs identified as having a major malformation risk above controls from highest to lower level of risk were (drug, with reported percent frequency in parentheses): valproate (8.9%), phenobarbital (5.9%), topiramate (4.4%), carbamazepine (3.0%), phenytoin (2.8%), lamotrigine (2.1%), and levetiracetam (2.0%). A recent systematic review of the literature similarly found that valproic acid, topiramate, phenobarbital, phenytoin, ethosuximide, and 11 polytherapies were significantly associated with major congenital malformations. Levetiracetam and lamotrigine did not significantly increase the risk of major congenital malformation.

A recent NAAPR analysis also showed that women taking AEDs for any indications are at a higher risk of delivering prematurely (<37 weeks) and giving birth to a small-for-gestational-age newborn. The Australian Pregnancy Register recently reported an increased risk of intrauterine fetal death when the fetus was exposed to AEDs, which was statically significant for carbamazepine. A prospective observational study from EURAP also found that the most important risk factor for intrauterine death (spontaneous abortion and stillbirth
combined) was maternal exposure to AED polytherapy and a parent with a history of major congenital malformation.\textsuperscript{84}

**NEUROMODULATION AND PREGNANCY**

Vagal nerve stimulation (VNS) therapy is an adjunctive therapy for patients with medically refractory epilepsy. Using data from EURAP\textsuperscript{85} in 26 pregnancies in women who received VNS therapy during pregnancy (the largest report to date), no evidence for teratogenicity was found. Another case series of four patients also reported the safety of VNS during pregnancy.\textsuperscript{86} In women with drug-resistant epilepsy who are planning future pregnancy and are not amenable to epilepsy surgery, VNS placement may be an option to be considered because this nonpharmacologic therapy may also enable simplification of the patient’s AED polytherapy regimen, thereby potentially reducing teratogenic risk. **CASE 6-1** illustrates several aspects of caring for a young woman with medically refractory catamenial epilepsy.

**Neurodevelopment and Fetal Antiepileptic Drug Exposure**

Exposure of the fetus to AEDs through the placenta may have adverse cognitive and behavioral effects, such as lower IQ, language deficits, autism, and attention deficit hyperactivity disorder. Several factors contribute to IQ scores, such as maternal IQ, maternal age, gestational age at birth, prenatal folic acid supplementation, socioeconomic status, and maternal use of tobacco or alcohol.

Meador and colleagues\textsuperscript{87} in the NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study reported that fetal valproic acid exposure was associated with a lower IQ and reduced cognitive abilities across a range of domains at 6 years of age in a dose-dependent manner. The adjusted mean IQ score of children exposed to high-dose (more than 800 mg/d) valproic acid was significantly lower than that of controls by 9.7 points. Exposure to other AEDs, including carbamazepine, lamotrigine, and phenytoin, was not associated with a lower IQ in children.

Adaptive Behavioral Scale assessments on children ages 3 years to 6 years exposed to valproic acid, lamotrigine, and carbamazepine in utero demonstrated

**FIGURE 6-3**

Risk of major congenital malformations in women taking an antiepileptic drug (AED) as monotherapy during pregnancy compared with women taking no AEDs based on the data provided by the North American Antiepileptic Drug Pregnancy Registry (NAAPR) (1997–2005).\textsuperscript{80}

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**KEY POINT**

- In counseling women with epilepsy who plan to become pregnant, the practitioners should discuss the need for staying on antiseizure medication, simplifying the medication regimen, attempting monotherapy, and selecting medications with a more favorable side effect profile.
CASE 6-1

A 19-year-old woman presented to a tertiary epilepsy center for evaluation of medically refractory epilepsy. She had developed viral encephalitis complicated by status epilepticus at 15 years of age requiring a medication-induced coma in an intensive care setting for 1 month. Eventually, she was discharged to rehabilitation. Her condition dramatically improved except for mild psychomotor slowing and development of medically refractory epilepsy, which clustered around her menstrual period.

At age 19, the patient was taking a combination of oxcarbazepine 1200 mg total daily dose, topiramate 200 mg total daily dose, and lamotrigine 600 mg total daily dose. She reported approximately 10 focal impaired awareness seizures per month, 7 of which clustered approximately 2 days before the onset of her menstrual period and 3 days afterward. A trial of progesterone lozenges, clobazam, and acetazolamide around the time of her menstrual period did not result in successful treatment of her catamenial seizures.

Because the patient was of reproductive age and sexually active, she was given a prescription for folic acid 1 mg/d and counseled to consider an intrauterine device with progesterone release for contraception.

Two years later, the patient informed her epileptologist that she was planning to marry and have a family. She wanted to plan in advance to reduce the risk of anticonvulsant medications on her future offspring. Epilepsy monitoring captured seizures of multifocal independent left and right hemispheric onset, indicating that she was not a candidate for epilepsy surgery. Topiramate was successfully weaned during inpatient monitoring, but subsequent attempts to streamline her antiepileptic drug polytherapy to monotherapy to reduce adverse effects resulted in increased seizure severity and frequency, especially surrounding the time of her menstrual periods.

She was counseled about the potential risks of polytherapy, and she elected to undergo vagal nerve stimulation (VNS) in the hope of further simplification of her antiseizure medication regimen. Approximately 6 months later and after multiple adjustments of the VNS settings, she finally was successfully weaned off oxcarbazepine and continued with lamotrigine monotherapy. Once seizures stabilized, a baseline lamotrigine serum level was obtained to guide future adjustments of her dose in case of pregnancy.

COMMENT

This patient had medically refractory catamenial epilepsy of multifocal origin that was not amenable to resective surgery. Unfortunately, she did not respond to targeted therapy for her hormonally exacerbated seizures, and further simplification of her antiseizure medications was not possible, putting her future pregnancy at risk of teratogenicity because of the antiepileptic drug polytherapy. VNS therapy has not been shown to adversely affect pregnancy outcome or carry additional risk for teratogenicity and provided a chance to achieve monotherapy in this patient with medically refractory catamenial epilepsy.
specific deficits in socialization, motor function, and a relative weakness in communication among children exposed to valproate, but not in those exposed to lamotrigine and carbamazepine. A systematic meta-analysis of 29 cohort studies found that valproate had similarly detrimental effects on neurodevelopmental outcomes, while oxcarbazepine and lamotrigine exposure was associated with an increased occurrence of autism.

**FOLIC ACID SUPPLEMENTATION**

Folic acid is essential during gestation because of its involvement in nucleic acid and amino acid synthesis, cell division, DNA methylation, and tissue growth. Some AEDs, such as valproic acid, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone, alter folic acid metabolism and may decrease folic acid levels in the blood. A randomized double-blind prevention trial conducted at 33 centers in seven countries by the Medical Research Council Vitamin Study Research Group determined that folic acid 4 mg/d supplementation around the time of conception can prevent neural tube defects. In this study, women with epilepsy were excluded. Other studies recently found that periconceptional folate supplementation has a positive association with a better neurodevelopmental outcome, a lower rate of autism spectrum disorder in the general population, and a higher IQ in children exposed to AEDs in utero. The US Public Health Service, Centers for Disease Control and Prevention, and AAN each recommend a dose of 0.4 mg/d of folate for all women of childbearing age to prevent neural tube defects. There are no solid data and, therefore, no specific recommendation regarding the benefits of higher doses of folic acid in women with epilepsy taking AEDs. A systematic review concluded that folic acid 5 mg/d in women without epilepsy may provide 85% protection against neural tube defects. However, a recent population-based study of 2302 mother-child pairs in Spain suggested that a dosage of folate above 1 mg/d may be associated with an increased risk of small-for-gestational-age newborns. In another analysis, more than 1 mg/d perinatal folate supplementation was associated with poorer cognitive development in children 4 years to 5 years old. Some experts have recommended the use of a higher folic acid dose of 4 mg/d to 5 mg/d in women taking valproic acid, carbamazepine, phenobarbital, phenytoin, and primidone; however, this practice is not uniform, and given contradictory data concerning higher-dose folic acid safety, further data are needed before adopting higher-dose folic acid use as a standard practice in the treatment of women with epilepsy who are receiving valproate or an enzyme-inducing AED.

**BREAST-FEEDING**

There are many known benefits of breast-feeding, including reduced risk of lower respiratory tract infections, atopic dermatitis, asthma, acute otitis media, gastroenteritis, obesity, diabetes mellitus, childhood leukemia, sudden unexpected death, and necrotizing enterocolitis in babies. Breast-feeding is also beneficial to the mother in reducing the risk of breast cancer, ovarian cancer, postpartum depression, and diabetes mellitus. All AEDs can be transmitted into the breast milk to some degree, but this amount is much less than that previously transmitted through the placenta to the fetus. The AED level transmitted to an infant via breast milk depends on multiple factors, including the amount of AED excreted into breast milk and AED absorption and clearance by the infant. The actual infant AED exposure from breast milk is usually low, and the benefits of breast-feeding
are ultimately felt to outweigh the potential risks for most women with epilepsy and their newborns. For barbiturates and benzodiazepines, the risk-benefit ratio should be evaluated more carefully because of the reports of sedation, lethargy, weight loss, and higher drug levels in the child than in the mother.

In an extension of the NEAD study, pregnant women with epilepsy who were taking a single AED (carbamazepine, lamotrigine, phenytoin, or valproate) during pregnancy were followed to focus on the effects of breast-feeding while receiving an AED on cognitive outcome of these children at age 3. A total of 42% of these women who were taking a single AED during pregnancy went on to breast-feed their newborns. Breast-fed children exposed to AEDs in utero and through breast milk exhibited higher IQs and enhanced verbal abilities compared with children exposed to AEDs in utero who were not breast-fed. Our present knowledge is not conclusive regarding the recommendation for breast-feeding in mothers taking AEDs, however. Current practice is to educate women with epilepsy regarding the known benefits of breast-feeding and potential risks for infant exposure to AEDs so that women can make an informed decision. Except for barbiturates and benzodiazepines, the reported side effects in infants who are breast-fed on other AEDs have been rare or infrequent, and the benefit may outweigh the risks.

PERIMENOPAUSE AND MENOPAUSE
Perimenopause is characterized by decreased ovarian progesterone secretion, leading to increased anovulatory menstrual cycles. Early in perimenopause, estrogen secretion remains high, creating an excitatory environment and contributing to seizure exacerbation. When menopause is achieved, because of diminished levels of follicle-stimulating hormone and a hypogonadal state, seizures stabilize. A recent questionnaire found that two-thirds of menopausal or perimenopausal women experiencing the early signs of menstrual changes reported seizure exacerbation. A history of catamenial epilepsy and the use of hormonal replacement therapy were associated with an increase in seizure frequency. Menopausal women generally report a decrease in seizure frequency.

A follow-up randomized, double-blind, placebo-controlled trial of hormone replacement therapy in menopausal women with epilepsy using 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone found that seizure frequency significantly increased in a dose-related manner with the use of hormone replacement therapy. The study was terminated because of an increased risk of breast cancer with this form of hormone replacement therapy.

For women with catamenial epilepsy who are at risk of seizure exacerbation during the perimenopause state, antiseizure medications may need to be adjusted to higher therapeutic levels. Once menopause is reached, AED doses may be reduced back to their baseline. The 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone formulation of hormone replacement therapy should be avoided in these patients. For women in whom hot flashes are disturbing sleep, consultation with the patient’s gynecologist is warranted to explore other hormonal treatment approaches.

BONE HEALTH
Some AEDs are identified as an independent risk factor for low bone density and secondary osteoporosis. The duration of epilepsy and cumulative drug load both correlate with a progressive reduction in bone mineral density, predisposing patients to fractures. Persons with epilepsy have a risk of fracture that is 2 to
6 times higher than that of the general population because of altered bone metabolism, decreased bone density, and a propensity to fall as a result of a seizure or AED-induced loss of balance.\(^99,10^5\) Risk factors for bone loss other than epilepsy and AEDs include female sex, postmenopausal status, sedentary lifestyle, smoking, excessive alcohol intake, inadequate sun exposure, and certain endocrine conditions. Many AEDs are known to alter bone metabolism, especially the enzyme-inducing AEDs.

The enzyme-inducing AEDs, such as phenytoin, phenobarbital, and primidone, are most consistently associated with a low bone mineral density and bone disorders.\(^10^1,10^2\) However, the data regarding the effect of valproic acid, carbamazepine, oxcarbazepine, lamotrigine, gabapentin, vigabatrin, levetiracetam, and topiramate on bone metabolism and bone density are limited and show conflicting results. Levels of vitamin D metabolites, such as 25-hydroxyvitamin D, may be low in people with epilepsy who are taking enzyme-inducing AEDs. Elevated bone turnover markers in these patients reflect increased bone remodeling, are associated with a higher rate of bone loss, and are an independent predictor of bone fracture.\(^99,10^1,10^3\)

Long-term gabapentin use in several studies was associated with bone loss in the hip and spine.\(^10^4–10^6\) Findings with carbamazepine, valproic acid, and lamotrigine are mixed. In one systematic review of the literature, only 3 of 11 carbamazepine monotherapy studies and 6 of 11 valproic acid monotherapy studies showed a significant reduction in bone mineral density.\(^10^7\) In a study of bone metabolism and density in premenopausal women with epilepsy receiving AED monotherapy (phenytoin, carbamazepine, valproic acid, and lamotrigine), phenytoin altered bone metabolism and increased bone turnover, while carbamazepine and valproic acid were associated with low calcium levels.\(^10^8\) Lamotrigine did not result in low calcium levels or increased bone turnover markers. A more recent study on adults treated with carbamazepine, oxcarbazepine, valproic acid, lamotrigine, topiramate, and levetiracetam monotherapy found reduced bone mineral density with levetiracetam and oxcarbazepine.\(^10^9\) Previous studies demonstrated decreased bone mineral density in children treated with oxcarbazepine.\(^11^0,11^1\) Another study found no harmful effects of levetiracetam on bone density, indicating the need for further research.\(^11^2\) **TABLE 6-4** summarizes our current knowledge about the effect of AEDs on bone turnover and bone mineral density.

Monitoring calcium and vitamin D metabolites is important in patients who take AEDs. Based on the Society for Endocrinology guidelines, 25-hydroxyvitamin D concentrations should be maintained at greater than 30 ng/mL, which may require at least 1500 IU/d to 2000 IU/d of vitamin D supplementation. Dual energy x-ray absorptiometry (DEXA) scans should be performed periodically to monitor bone mineral density. If osteopenia or osteoporosis is detected, consideration should be given to starting bisphosphonates or other therapeutic agents, increasing calcium and vitamin D supplementation, and/or replacing enzyme-inducing AEDs. The patient may benefit from a referral to an endocrinologist. Other treatment options for osteoporosis may include estrogens and hormonal therapy, parathyroid hormone (teriparatide), and estrogen agonist/antagonist (raloxifene). **TABLE 6-5** summarizes the suggested considerations in the management of women with epilepsy at risk of osteoporosis. **CASE 6-2** demonstrates some important points in counseling a woman of menopausal age.
**TABLE 6-4**

Effect of Antiepileptic Drugs on Bone Mineral Density and Bone Turnover (Based on Majority of Studies)

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Lowering Bone Mineral Density/Affecting Bone Metabolism</th>
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</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Yes</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Yes</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Yes</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>No</td>
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<tr>
<td>Levetiracetam</td>
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<tr>
<td>Oxcarbazepine</td>
<td>Yes</td>
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<tr>
<td>Phenobarbital</td>
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<td>Phenytoin</td>
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<td>Primidone</td>
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<td>Topiramate</td>
<td>Maybe</td>
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<tr>
<td>Valproic acid</td>
<td>Yes</td>
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<tr>
<td>Zonisamide</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**TABLE 6-5**

Recommendations for Women With Epilepsy at Risk of Osteoporosis

If Osteopenia or Osteoporosis Is Not Detected

- Monitor calcium and vitamin D levels 1 to 2 times per year
- Follow bone density (dual energy x-ray absorptiometry [DEXA] scan), every 2 years, especially if postmenopausal
- Consider calcium (at least 1200 mg/d) and vitamin D (at least 600 IU/d) supplements or greater amounts to achieve a level of >30 ng/mL
- Encourage weight-bearing exercises
- Encourage cessation of smoking
- Suggest limiting alcohol consumption
- Recommend avoiding excessive caffeine

If Osteopenia or Osteoporosis Is Detected

- Increase vitamin D supplement to 1500–2000 IU/d to achieve a level of >30 ng/mL
- Lifestyle modifications to decrease the risk of falls and fractures
- Discuss advantages and disadvantages of switching to another non-enzyme-inducing antiseizure medication
- Consider bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid)
- Consider estrogens and hormone therapy, parathyroid hormone (teriparatide), and estrogen agonist/antagonist (raloxifene)
- Consider referring to an endocrinologist
A 52-year-old postmenopausal woman, who had been seizure free on oxcarbazepine for 10 years, presented with osteoporosis of her lumbar spine and hip that had been diagnosed by her primary care physician. Her seizures had started at the time of puberty and occurred in clusters for about 3 days of the month around the time of her ovulation. She had a feeling of déjà vu and a rising butterfly sensation in her stomach followed by confusion. There were rare instances of progression of focal impaired awareness to bilateral tonic-clonic seizures. The patient had first been tried on phenytoin, to which she developed bleeding of her gums while brushing teeth and gingival hyperplasia. Her seizures did not respond to valproic acid. Finally, oxcarbazepine was started, and once the dose was adjusted to high therapeutic levels, she became seizure free.

She presented to discuss her options and plan of care. Her vitamin D level was low at 20 ng/mL. Long-term inpatient video-EEG monitoring while the patient was tapered off oxcarbazepine showed independent left and right temporal interictal sharp waves. Four seizures were captured, one from the left anterior temporal area and three from the right anterior and middle temporal region. Her medication was switched over the course of 2 months to lamotrigine, and she was started on vitamin D 2000 IU/d with 1200 mg of calcium. Weight-bearing exercises were encouraged, and the patient was referred to endocrinology and started on bisphosphonate therapy. The patient’s seizures responded to lamotrigine, and a repeat bone density study showed significant improvement in bone mineral density over the next 2 years.

This case highlights the added risk of hepatic enzyme–inducing antiepileptic drugs such as oxcarbazepine in accelerating bone loss and compromising bone health in women with epilepsy. One challenge is the risk of seizure recurrence when trying to switch the patient from a hepatic enzyme–inducing antiepileptic drug. There is no guarantee that the patient will remain seizure free, and seizure recurrence may result in significant patient safety, social, and psychological consequences. Up to 21.7% of patients switched from phenytoin and carbamazepine to other antiseizure medications are at risk of seizure recurrence within 6 months of the switch.113 The inpatient epilepsy monitoring in this patient suggested a very limited possibility for seizure freedom off anticonvulsant therapy. Fortunately, her seizures responded to lamotrigine, and with proper vitamin D and calcium replacement and bisphosphonate therapy, the patient’s osteoporosis improved.
CONCLUSION
The professionals who care for women with epilepsy should be aware of the challenges these women are facing because of complex hormonal interactions with their antiseizure medications and seizure disorders. In every step of their lives from puberty, menses, and birth control to conception, pregnancy, childbirth, breast-feeding, childcare, bone health, and menopause, women with epilepsy need to be educated to make informed decisions. Practitioners need to keep up-to-date with the latest treatment recommendations to help women with epilepsy live safe and productive lives.

REFERENCES


